UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

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Executive Summary

The Health Effects Division (HED) Permethrin Registration Review Team has evaluated the status of the human health assessment for the insecticide permethrin to determine the scope of work necessary to support Registration Review. Permethrin is a broad-spectrum pyrethroid insecticide that is registered in the U.S. for use in a wide variety of residential settings, on a wide variety of crops, and also as a pediculicide for the treatment of head lice and scabies. It was first registered on February 25, 1979. The most recent risk assessment for permethrin was completed in 2009 as part of reregistration elgibility decision (C. Smith, D357566, 04/01/2009). Based on the current use profile, exposures can be expected to occur via the dietary (food and drinking water), residential (handler

and postapplication), and occupational (handler and postapplication) routes for permethrin.

The toxicity database for permethrin is complete at the present time with the exception of an immunotoxicity study. The Food Quality Protection Act (FQPA) safety factor (SF) for permethrin will need to be re-evaluated during registration review following a final determination of the potential for increased susceptibility of infants and children to pyrethroid pesticides based on the results of all available data. Upon receipt of the immunotoxicity study, HED will reevaluate the points of departure and uncertainty factors for the dietary and occupational exposure assessments.

Permethrin is among the group of 58 pesticide active ingredients on the initial list to be screened under the Endocrine Disruptor Screening Program (EDSP) and has been issued an order to conduct the Tier 1 testing. Once all required Tier 1 and Tier 2 data have been received and reviewed, the endpoints and safety factors used for risk assessment purposes will be examined and a new risk assessment performed if necessary.

The existing residue chemistry database for permethrin is adequate for risk assessment purposes. The qualitative nature of the residue(s) of permethrin in plants and animals has been adequately identified/characterized and is understood. The residues of concern in plants and animals include cis- and trans-permethrin for purposes of both tolerance assessment and risk assessment. The acute, chronic non-cancer, and chronic cancer dietary analyses from the 2009 permethrin risk assessment are considered highly refined estimates of dietary exposure. All calculated dietary risk estimates were below the Agency's level of concern. New acute, chronic non-cancer, and chronic cancer dietary risk assessments may need to be conducted during registration review. The assessments should include updated consumption information, any revised toxicological points of departure, and utilize the newest version of Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID). Additionally, should a review of the USDA Pesticide Data Program (PDP) and percent crop treated information show that exposure may be increasing, revised anticipated residues may need to be generated and incorporated into the acute and chronic dietary risk assessments.

The residential exposure database is adequate to support the registration review process for permethrin. In the 2009 risk assessment, all of the non-cancer residential handler and postapplication risk estimates and almost all of the cancer residential handler and postapplication risk estimates were below the Agency's level of concern. An updated residential exposure assessment may be required under registration review based upon revisions to HED's Residential Standard Operating Procedures (SOPs) which was reviewed by the Scientific Advisory Panel (SAP) in October 2009. An updated assessment may also be required if new data are identified which impact exposure estimates, new points of departure, a revised FQPA SF, or revisions to exposure policies and procedures are made.

In the 2009 permethrin risk assessment, HED performed acute, short- and intermediate-term, chronic, and cancer aggregate risk assessments. All of the aggregate scenarios that were assessed did not result in aggregate risks of concern, with the exception of the combined turf/indoor carpet broadcast spray exposure scenario to toddlers in the short-

and intermediate-term aggregate assessment. An updated aggregate exposure and risk assessment may be required under registration review if dietary or residential exposure estimates are updated or revisions are made to the permethrin points of departure or FQPA SF.

The occupational exposure database is adequate to support the registration review process for permethrin. In the 2009 risk assessment, all of the non-cancer occupational handler risk estimates and almost all of the cancer occupational handler risk estimates were below the Agency's level of concern at some level of risk mitigation. In the 2009 risk assessment, all of the non-cancer and cancer occupational postapplication risk estimates were below the Agency's level of concern. An updated occupational exposure assessment may be required under registration review if new data are identified which impact exposure estimates, new points of departure are selected, or if revisions to exposure policies and procedures are made.

Introduction

Permethrin is a broad spectrum synthetic pyrethroid insecticide used to control a variety of insects. HED has reviewed the most recent exposure and risk assessments for permethrin, as well as toxicity data, exposure and usage databases, and the latest Agency science policy and risk assessment methodologies to determine if sufficient data are available and if updates are needed to support registration review. Additionally, the team conducted a screening-level literature search for any information that would aid in assessing human health risks to permethrin.

Chemical Identity

Permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] is a broad spectrum, non-systemic, synthetic pyrethroid insecticide registered for use on numerous food/feed crops, livestock and livestock housing, modes of transportation, structures, buildings (including food handling establishments), and for residential uses. Permethrin is formulated as an emulsifiable concentrate, a wettable powder (including water soluble bags), a granular, a dust, as well as a number of ready to use formulations, such as aerosol cans, foggers, trigger pump sprayers, ear tags, etc.

In addition to the pesticidal uses, there is also a non-Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) pharmaceutical use of permethrin as a pediculicide for the treatment of head lice and scabies. The Food and Drug Administration (FDA) approves uses of the pesticidal-containing pharmaceutical products under the Federal Food, Drug, and Cosmetic Act (FFDCA).

The chemical structure and nomenclature of permethrin and the physicochemical properties of technical grade permethrin are presented in Tables 1 and 2.

Hazard Identification/Toxicology

As with the other pyrethroids, permethrin causes neurotoxicity in insects and mammals by the modulation of nerve axon sodium channels. Pyrethroids interfere with the ability of the nervous system to relay nerve transmissions, potentially resulting in tremors, convulsions, salivation, and other clinical effects.

The toxicity database for permethrin is complete at the present time with the exception of an immunotoxicity study (see Table 4). Permethrin has a low acute toxicity via the oral, dermal, or inhalation route of exposure. Permethrin is not an eye or skin irritant and not a skin sensitizer.

For a summary of the subchronic and chronic toxicity profile, see Table 3C. The critical effect for permethrin (i.e., neurotoxicity) is based on the most sensitive species, rats. The effects of permethrin in several species are early in onset and short-term, without indications that incidence or severity of effects would increase based on metabolism studies that permethrin is rapidly absorbed, metabolized, and almost completely eliminated from the body within a short period of time. The oral exposure limits for all durations were based on an acute neurotoxicity study in rats. The dermal exposure limits for all durations were based on a 21-day rat dermal toxicity study. The inhalation exposure limits for all durations were based on a rat 15-day inhalation study.

As part of the 2009 risk assessment, the Agency requested that a DNT study be conducted on rats with permethrin. This request was based on evidence of neurotoxicity in the acute and subchronic neurotoxicity studies and other subchronic and chronic toxicity studies in dogs and rats. Increased incidence of microscopic lesions associated with neurotoxic effects at high doses in the subchronic neurotoxicity studies further supported this request. However, based on the Agency's review of existing pyrethroid data, EPA has come to the conclusion that the DNT is not a particularly sensitive study for comparing the sensitivity of young and adult animals to pyrethroids. The science supporting this conclusion can be found in "*Pyrethroids: Evaluation of Data from DNTs & Consideration of Comparative Sensitivity"* (E. Scollon, 1/20/10, D371723), available at http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html. In an effort to ensure the highest level of protection of infants and children, the Agency plans to continue reviewing scientific data regarding the potential increased susceptibility of pyrethroid pesticides as it becomes available.

The total uncertainty factor for permethrin is currently 100X (1X FQPA Safety Factor, and 10X for inter-species variation, and 10X for intra-species variation). The FQPA safety factor was reduced to 1X because: (1) the toxicity database is adequate to characterize the potential for pre- and postnatal risk for infants and children; (2) no reproductive or developmental effects were observed in rats; and (3) there is no evidence (qualitative or quantitative) for increased susceptibility following *in utero* and/or pre-/post-natal exposure in the developmental toxicity studies in rats and rabbits and multi-generation reproduction studies in rats. The FQPA factor for permethrin will be re-evaluated during registration review following a final determination of the potential for increased susceptibility of infants and children to pyrethroid pesticides based on the results of all available data.

Permethrin is classified as "Likely to be Carcinogenic to Humans" by the oral route based on evidence of two reproducible benign tumor types (lung and liver) in the mouse, equivocal evidence of carcinogenicity in Long-Evans rats, and supportive SAR information. Mutagenicity studies did not demonstrate any evidence of mutagenic potential for permethrin.

For a summary of the relevant toxicological endpoints and points of departure used in risk assessment, please see Tables 3D (dietary and residential endpoints) and 3E (occupational endpoints).

Endocrine Disruption Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), permethrin is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. Permethrin was included on that list and has been issued an order to conduct the Tier 1 testing. Once all required Tier 1 and Tier 2 data have been received and reviewed, the endpoints and safety factors used for permethrin risk assessment purposes will be examined and a new risk assessment performed if necessary. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Conclusions for Hazard Identification/Toxicology

The toxicity database for permethrin is complete at the present time with the exception of an immunotoxicity study (see Table 4). The FQPA SF for permethrin will be re-evaluated during registration review following a final determination of the potential for

increased susceptibility of infants and children to pyrethroid pesticides based on the results of all available data.

Residue Chemistry

Permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] is a synthetic pyrethroid insecticide. The existing residue chemistry database for permethrin is adequate for risk assessment purposes. No additional data are required at this time pending receipt and review of residue chemistry data required to resolve deficiencies outlined in the most recent residue chemistry chapter for permethrin (S. Kinard, D313662, 03/17/2005). These studies were required in the 2009 Permethrin DCI (GDCI-109701-26467). HED has received and reviewed a portion of the required studies (D. Wilbur, D382837, D382842, D382844, 01/26/2011). The remaining outstanding studies include:

- OPPTS 860.1500 (Crop Field Trials) for cabbage; collards; grass, forage; lettuce, leaf; soybean, forage; and soybean, seed.

The qualitative nature of the residue(s) of permethrin in plants and animals has been adequately identified/characterized and is understood. The residues of concern in plants and animals include *cis*- and *trans*-permethrin for purposes of both tolerance assessment and risk assessment. Adequate methods are available for the enforcement of established tolerances, as currently defined. Adequate analytical methods exist for data collection. Adequate storage stability, processed food, and magnitude of the residue data exist.

Conclusions for Residue Chemistry

The residue chemistry database for permethrin is complete at the present time with the exception of the outstanding data required in the 2009 GDCI.

Dietary Exposure and Risks

Acute, chronic, and cancer dietary (food and water) exposure risk assessments were conducted (S. Ary, D325429, 02/01/2006) using the DEEM-FCID™, Version 2.03 model, which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The dietary risk assessment incorporated all available information, including: usage data (percent crop treated), anticipated residues (ARs) based on field trial data, and ARs based on USDA Pesticide Data Program (PDP) monitoring data. Estimated drinking water concentrations were directly incorporated into the dietary exposure assessments.

Drinking Water

The Environmental Fate and Effects Division used Tier-II modeling to generate estimated environmental concentrations (EECs) in surface water (J. Melendez, D324197, 1/17/2006). Only surface water values (as opposed to groundwater values) were used in the acute and chronic assessments as these represent upper bound concentrations that would be expected in drinking water. The EDWCs for permethrin were calculated based on a maximum application rate of 2.0 lb ai/A. The concentration used in the acute dietary assessment was calculated from surface water at 0.00479 ppm. The concentrations used in the chronic and cancer dietary assessments were calculated from surface water at 0.000901 ppm and 0.000751 ppm, respectively, using the Georgia onion scenario. The chronic value represents the mean value over a 30-year period and is a high end estimate

that is 1.7 times the next lowest scenario, California lettuce at 0.000545 ppm. The cancer value also represents the mean value over a 30-year period and is a high end estimate that is 1.6 times the next lowest scenario, California lettuce at 0.000475 ppm. Water residues were incorporated in the DEEM-FCID™ into the food categories "water, direct, all sources" and "water, indirect, all sources". Given the conservative nature of the 2006 EFED drinking water assessment, HED does not anticipate the need for a new drinking water estimates during registration review.

Acute Dietary Exposure and Risk (Food and Drinking Water)

A highly refined probabilistic (Monte-Carlo) acute dietary exposure assessment was conducted to estimate the dietary risks (S. Ary, D325429, 02/01/2006). Permethrin residue estimates used in this assessment included *cis*- and *trans*-permethrin, calculated as total permethrin, along with the percent crop treated (%CT) estimates reported by the Biological and Economic Analysis Division (BEAD). The anticipated residue (AR) estimates are based primarily on the USDA PDP monitoring data (PDP data). Tolerance values were used for livestock commodities. DEEM 7.81 default processing factors were used in this assessment for several commodities along with the available data from the processing studies. Acute dietary risk estimates are provided for the general U.S. population and various population subgroups, with the major emphasis placed on the exposure estimates for infants and children. This assessment concluded that for all supported registered commodities, the acute dietary risk estimates did not exceed HED's level of concern (less than 100% of the aPAD) at the 99.9^{th} exposure percentile for the U.S. population (4% of the aPAD) and all population subgroups, with the highest exposed population subgroup being all infants less than 1 year old at 16% of the aPAD.

Chronic Non-Cancer

A highly refined chronic dietary exposure assessment was conducted to estimate the dietary risks associated with permethrin (S. Ary, D325429, 02/01/2006). Permethrin residue estimates used in this assessment include *cis*- and *trans*-permethrin, calculated as total permethrin, along with the %CT estimates reported by BEAD. The AR estimates are based primarily on the PDP data. Feeding studies along with %CT on feed items and dermal studies were used to calculate AR estimates for livestock commodities if PDP data were not available. DEEM 7.81 default processing factors were used in this assessment for several commodities along with the available data from the processing studies. Chronic dietary risk estimates are provided for the general U.S. population and various population subgroups, with the major emphasis placed on the exposure estimates for infants and children. This assessment concluded that for all supported registered commodities, the chronic dietary risk estimates did not exceed HED's level of concern (less than 100% of the cPAD) for the U.S. population and all population subgroups (all were less than 1% of the cPAD).

Chronic Cancer

A highly refined cancer dietary exposure assessment was conducted to estimate the dietary risks of permethrin. Permethrin residue estimates used in this assessment include *cis*- and *trans*-permethrin, calculated as total permethrin, along with the %CT estimates reported by BEAD. The AR estimates are based primarily on the PDP data. Feeding studies along with %CT on feed items and dermal studies were used to calculate AR estimates for livestock commodities if PDP data were not available. DEEM 7.81 default

processing factors were used in this assessment for several commodities along with the available data from the processing studies. The estimated exposure of the general U.S. population to permethrin is 0.000117 mg/kg/day. Applying the Q_1* of 9.567 x 10^{-3} $(mg/kg/day)^{-1}$ to the exposure value results in a cancer risk estimate of 1.1 x 10^{-6}.

Conclusions for Dietary Exposure and Risk Assessment
An updated dietary risk assessment may be required during the registration review process to further refine residues in drinking water and food, and any revised points of departure (PoDs) or uncertainty factors. The revised assessments should include updated consumption information and will utilize the newest version of DEEM-FCID. Additionally, should a review of the PDP and other relevant information show that exposure may be increasing, revised anticipated residues may need to be generated and incorporated into the dietary risk assessments.

Residential Exposure and Risks
Permethrin is registered for use in a variety of indoor and outdoor residential environments including: lawns, gardens, indoor surfaces and spaces, ornamentals, and on pets. Due to this use profile, adult residential homeowners may experience exposure to permethrin during application of the chemical (i.e., residential handler exposures). Adults and children may experience exposure to permethrin when contacting permethrin-treated areas (i.e., residential postapplication exposure).

In addition to homeowner uses in residential settings, permethrin is labeled for mosquito adulticide use, which is applied by occupational handlers, but may result in postapplication exposures in residential settings. Permethrin is also used in residential automatic misting systems for mosquito control, as well as impregnated into clothing which also may result in occupational handler exposure and residential postapplication exposure.

The most recent permethrin risk assessment (C. Smith, D357566, 04/01/2009) addressed the potential residential handler exposures to adults and the potential residential postapplication exposures to adults and children of varying ages.

<u>Residential Handlers</u>
There are hundreds of permethrin products currently registered for use by homeowners. The 2009 risk assessment assessed 25 residential handler scenarios which reflect the major residential uses of permethrin based on types of application equipment. Residential handler exposures were estimated using exposure data from a number of data sources, including: the Pesticide Handler Exposure Database (PHED), the Outdoor Residential Task Force (ORETF), the Non-Dietary Exposure Task Force (NDETF), the Chemical Manufacturers Association (CMA) Antimicrobial Exposure Assessment Study, and four proprietary exposure studies.

The non-cancer handler risk estimates presented in the 2009 risk assessment indicate that all of the residential handler scenarios resulted in risks that did not exceed HED's level of concern (i.e., MOEs > 100).

A residential handler cancer risk assessment was also conducted as part of the 2009 risk assessment. The same scenarios, assumptions, and exposure data were used as in the non-cancer assessment. HED estimated cancer risks assuming a maximum of 1 day of exposure per year which resulted in cancer risk estimates ranging from 1.6×10^{-11} to 7.4×10^{-7}. In addition, HED calculated the maximum number of days of handler exposure per year that still would result in cancer risks less than or equal to 1×10^{-6}. Four scenarios resulted in 5 days or less of allowable handler exposure. 5 days was used as the target based on survey data from the *Residential Exposure Joint Venture (REJV)* that showed that homeowners use permethrin products on an average of 5 times a year.

Residential Postapplication

Permethrin can be used in many areas that can be frequented by the general population including residential areas. As a result, individuals can be exposed by entering these areas if they have been previously treated. Permethrin can also be used on companion animals, which can lead to exposures by contact with the treated animals.

In the 2009 risk assessment, a number of postapplication residential exposure scenarios were assessed for adults and children. These scenarios included playing on a treated lawn (adults and children), playing on a treated indoor surface (adults and children), playing with treated companion animals (children only), wearing permethrin impregnated clothing (adults and children), working in a treated garden, mowing (adults only), and mosquito treatments (adults and children). For adults, dermal exposures were assessed for all scenarios except for mosquito treatments where inhalation was the focus. Children dermal and non-dietary ingestion exposures were assessed for all scenarios except the mosquito treatments where inhalation was the focus.

Residential postapplication exposures were estimated using exposure data from a number of data sources, including: the ORETF, the NDETF, and a number of proprietary exposure studies. The non-cancer postapplication risk estimates presented in the 2009 risk assessment indicate that all of the adult (dermal and inhalation) and children (dermal, inhalation, and non-dietary ingestion) residential postapplication scenarios resulted in risks that did not exceed HED's level of concern (i.e., MOEs > 100). HED also performed a combined residential postapplication assessment by combining children's dermal and non-dietary ingestion exposures for turf (i.e., dermal, hand-to-mouth, object-to-mouth, and soil ingestion), indoors (i.e., dermal and hand-to-mouth), pets (i.e., dermal and hand-to-mouth), and impregnated clothing (i.e., dermal and object-to-mouth). All of these combined postapplication residential scenarios resulted in risks that did not exceed HED's level of concern (i.e., MOEs > 100).

An adult residential postapplication cancer risk assessment was also conducted as part of the 2009 risk assessment. The same scenarios, assumptions, exposure data were used as in the non-cancer postapplication assessment. HED estimated cancer risk assuming estimates for an annual a maximum of 1 day of exposure per year. The estimates represent one day of postapplication exposure per year and exposure on the day of application (i.e., day 0) for each year of a 50-year exposure period. Cancer risk estimates ranged from 9.2×10^{-10} to 8.4×10^{-7}. In addition, HED calculated the maximum number of days of handler exposure per year that still would result in cancer risks less than or

equal to $1x10^{-6}$. Three indoor scenarios resulted in 5 days or less of allowable postapplication exposure.

Conclusions for Residential Exposure and Risk Assessment
The residential exposure database is adequate to support the registration review process for permethrin. An updated residential exposure assessment may be required under registration review based upon revisions to HED's Residential SOPs which was reviewed by the Scientific Advisory Panel (SAP) in October 2009. An updated assessment may also be required if new data are identified which impact exposure estimates, new points of departure, a revised FQPA SF, or revisions to exposure policies and procedures are made.

Aggregate Risk Assessment
In the 2009 permethrin risk assessment, HED determined that acute, short- and intermediate-term, chronic, and cancer aggregate risk assessments were appropriate. The acute and chronic aggregate assessments were equivalent to the acute and chronic dietary risk assessments. The acute and chronic dietary risk estimates for the general population and all population subgroups were not of concern to HED.

For the short- and intermediate-term aggregate assessment, HED examined a number of possible residential combined scenarios including turf/indoor surfaces, turf/vegetable gardens, and turf/pets to represent a variety of high-end, health protective residential adult and toddler exposures. These combined residential exposures were then combined with the chronic dietary exposures. HED concluded that, except for the combined turf/indoor carpet broadcast spray exposure to toddlers, the combined residues of permethrin from food, drinking water, and other potential residential exposures do not result in short- and intermediate-term aggregate risks of concern.

For the cancer aggregate assessment, HED examined a number of possible residential combined scenarios including turf/indoor surfaces and turf/vegetable gardens to represent a variety of high-end, health protective residential adult exposures. These combined residential exposures were then combined with the cancer dietary exposures. HED concluded that combined residues of permethrin from food, drinking water, and other potential residential exposures do not result in cancer aggregate risks of concern.

Conclusions for Aggregate Exposure and Risk Assessment
An updated aggregate exposure and risk assessment may be required under registration review if dietary or residential exposure estimates are updated. An updated assessment may also be required if new data are identified which impact the permethrin points of departure, the FQPA safety factor for permethrin, or if revisions are made to any exposure or risk assessment policies and procedures.

Occupational Exposure and Risks
Permethrin is registered for numerous food/feed crops, livestock and livestock housing, modes of transportation, structures, and buildings (including food handling establishments). Based on these uses, there is a potential for exposure to permethrin in occupational scenarios from handling permethrin products during the application process (i.e., mixer/loaders, applicators, flaggers, and mixer/loader/applicators) and a potential

for postapplication worker exposure from entering into areas previously treated with permethrin. The most recent permethrin risk assessment (C. Smith, D357566, 04/01/2009) included risk estimates for both occupational handler and occupational postapplication scenarios.

Occupational Handlers

Due to the scope of the various permethrin occupational uses (there are hundreds of registered permethrin products); the 2009 risk assessment evaluated 39 occupational handler scenarios to represent the major permethrin occupational handler scenarios based on application equipment and formulation. Occupational handler exposures were estimated using exposure data from a number of data sources, including: PHED, the ORETF, the CMA, and two proprietary exposure studies.

The non-cancer handler risk estimates presented in the 2009 risk assessment indicate that all of the occupational handler scenarios resulted in risks that did not exceed HED's level of concern (i.e., MOEs > 100) at some level of risk mitigation.

An occupational handler cancer risk assessment was also conducted as part of the 2009 risk assessment. The same scenarios, assumptions, and exposure data were used as in the non-cancer assessment. HED estimated cancer risks assuming a maximum of 10 days of exposure per year based on data from a Biological & Economic Analysis Division (BEAD) memo dated March 24, 2004 (D. Brassard, 03/24/04). Cancer risk estimates ranged from 5.4×10^{-11} to 1.1×10^{-4} depending on the level of risk mitigation.

Occupational Postapplication

The Agency has determined that there is the potential for occupational postapplication exposures to individuals entering fields treated with permethrin as well as individuals who wear (i.e., military battle dress) or make (i.e., garment workers) permethrin impregnated clothing. The 2009 risk assessment assessed all of these occupational postapplication scenarios.

In the 2009 risk assessment, the non-cancer occupational postapplication risk estimates for agricultural fields were estimated using permethrin specific dislodgeable foliar residue (DFR) data collected on cotton and peaches. This assessment also used surrogate transfer coefficient data from the Agricultural Reentry Task Force (ARTF) database. For all agricultural postapplication exposure scenarios, non-cancer risks did not exceed HED's level of concern (i.e., MOEs > 100) on the day of application – approximately 12 hours following application. No chemical specific exposure data was available for estimating occupational postapplication risk estimates for individuals who wear or make permethrin impregnated clothing. All non-cancer postapplication exposure scenarios for permethrin-impregnated clothing did not exceed HED's level of concern (i.e., MOEs > 100).

An occupational postapplication cancer risk assessment was also conducted as part of the 2009 risk assessment. The same scenarios, assumptions, and exposure data were used as in the non-cancer assessment. HED estimated agricultural postapplication cancer risks assuming individuals employed solely by one establishment (i.e., "hired hands") are exposed 10 days per year and individuals employed by multiple establishments (i.e.,

commercial or migratory farmworkers) are exposed 30 days per year. Occupational postapplication cancer risks for "hired hands" ranged from 6.9×10^{-9} to 1.4×10^{-6} and those for "commercial/migratory farmworkers" ranged from 9.9×10^{-8} to 1.0×10^{-6}. HED estimated postapplication cancer risks from wearing impregnated clothing by calculating an average residue assuming that the uniforms are worn 7 days between washes with a total of 30 washes. Occupational postapplication cancer risk estimates for individuals who wear or make permethrin impregnated clothing ranged from 3.6×10^{-6} to 1.2×10^{-6}.

Conclusions for Occupational Exposure and Risk Assessment
The occupational exposure database is adequate to support the registration review process for permethrin. Updated occupational handler exposure assessments may be required under registration review based upon revisions to the Agency's scenario-specific surrogate handler exposure data (http://www.epa.gov/pesticides/science/handler-exposure-table.pdf). Updated occupational postapplication exposure assessments may also be required under registration review based upon revisions to the dermal transfer coefficients from the Science Advisory Council for Exposure Policy Number 3 (http://www.epa.gov/pesticides/science/exposac_policy3.pdf). Revised occupational handler and postapplication assessments may also be needed if toxicological endpoints change or other new data are received by the Agency which impact exposure estimates.

Human Studies
Permethrin risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. Studies such as PHED, ORETF, NDETF, and the ARTF have been reviewed by the Agency and found on the basis of available evidence to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. The permethrin risk assessment also utilizes a number of chemical specific studies (see Table 6) which were also reviewed by the Agency and found on the basis of available evidence to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no barrier in EPA's "Protection of Human Subjects" regulation to reliance on any of these studies.

Public Health and Pesticide Epidemiology Data
An updated review of permethrin incident reports was recently prepared by HED (K. Oo, D386498, 03/01/2011). For this evaluation, the OPP Incident Data System (IDS) was consulted for pesticide incident data on the active ingredient permethrin. Permethrin data from the Agricultural Health Study (AHS) were also considered.

The IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6 (a) (2) reports from registrants, other federal and state health and environmental agencies and individual consumers. IDS contain reports from across the U.S. and most incidents have all relevant product information recorded. Reports submitted to the IDS represent anecdotal reports or allegations only, unless otherwise stated in the report. IDS records incidents resulting in higher severity outcomes in more detail, in a module called

the Main IDS module. This system stores incident data for death, major and moderate incidents, and it includes more details about the location, date and nature of the incident.

For IDS aggregate summaries, from January 1, 2002 to February 2011, there are 9992 cases reported for permethrin. Because it falls within the categories reported as counts (which includes minor, unknown or no effects), there is no unique report that provides details about the incident and single chemical incidents are not distinguished from multiple chemical incidents; however, a high frequency of incidents indicates there is a high potential for exposure and vice versa. For the Main IDS, from January 1, 2002, to February 1, 2011, there are 2478 cases reported that involve the active ingredient permethrin. Of these 2478 cases, there are 432 cases reported for single chemical permethrin only in the database and of these there were 5 deaths (HA) and 15 human majors (HB). These are summarized in more detail in the 2011 HED permethrin incident report.

The AHS is an epidemiology investigation (prospective cohort study) of health effects experienced by pesticide applicators in the states of Iowa and North Carolina. A main strength of the study is the ability to determine exposure to pesticides before cancer cases are diagnosed which distinguishes this study from other types of epidemiological investigations. Within the last three years, researchers with the AHS have produced several investigations of both cancer and non-cancer outcomes associated with use of permethrin on both livestock and crops (Rusiecki et al. 2008; Hoppin et al. 2008; Slager et al. 2010; and, Koutros 2010). The Agency will consider and review this data further as appropriate during registration review.

Based on the number of incidents reported for permethrin, the effects noted in the incidents, and the available AHS data; permethrin warrants further incident analysis during registration review. This further analysis will include reviewing permethrin incident data from other sources (such as, SENSOR and PCC) as well as cases studies and a medical literature search on human health effects of permethrin.

Tolerance Assessment and International Harmonization

Tolerances are established under 40 CFR §180.378 for residues of the insecticide permethrin, including its metabolites and degradates, in or on a variety of food and feed crops. A table with the US tolerances, the Canada MRLs, Mexico MRLs, and Codex MRLs for permethrin in registered RACs is provided in Table 5. These tolerances and MRLs are based on the residue analysis of permethrin.

Both Codex and Canada have established MRLs for permethrin. In most cases, the Codex and Canadian MRLs differ from each other as well as from the U.S. tolerance. Where possible, the Agency will work to harmonize tolerances/MRLs during registration review.

The current tolerance expression as listed in the 40 CFR §180.378 has not been updated to reflect current HED policies. The tolerance expression will need to be revised during the registration review process. The revised tolerance expression should be as follows:

"Tolerances are established under 40 CFR §180.378(a) for residues of the insecticide permethrin, including its metabolites and degradates, in or on a variety of food and feed crops. Compliance with the tolerance levels specified is to be determined by measuring only permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate], as the sum of its cis- and trans- isomers in or on the commodity".

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/compliance/resources/policies/ej/exec_order_12898.pdf. The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these high exposures indicate potential risks of concern, OPP will further refine the risk assessments to ensure that the risk estimates are based on the best available information.

Cumulative Risk Assessment

Permethrin is a member of the pyrethroid class of insecticides. This class also includes cyfluthrin, cypermethrin, deltamethrin, fluvalinate, bifenthrin, fenpropathrin, and lambda-cyhalothrin, among others. EPA developed a draft science policy document on the proposed common mechanism of toxicity for naturally-occurring pyrethrins and synthetic pyrethroids (Proposed common mechanism grouping for the pyrethrins and pyrethroids, draft, May 19, 2009; http://www.regulations.gov/search/Regs/home.html#documentDetail?R=09000064809a62df). This document was supported by the FIFRA Scientific Advisory Panel (SAP) and EPA will finalize the policy document on the pyrethroid common mechanism of toxicity taking into account the SAP comments. Pesticides with a common mechanism of toxicity are subject to cumulative risk assessment under the FQPA. Research is ongoing by EPA's Office of Research and Development (ORD) to make improvements to the SHEDS Probabilistic Exposure Model which are important for the cumulative risk assessment. EPA ORD is also developing physiologically-based pharmacokinetic models for several pyrethroids. The status of both of these research modeling efforts was reviewed by the FIFRA SAP in July, 2010 and meeting materials are available in the docket at (http://www.regulations.gov/search/Regs/home.html#docketDetail?R=EPA-HQ-OPP-2010-0378). For information regarding EPA's efforts to evaluate the risk of exposure to pyrethroids, refer to http://www.epa.gov/pesticides/cumulative/.

Data Requirements

HED does not anticipate that additional residue chemistry, toxicology or occupational/residential exposure data will be required for the permethrin registration review process, with the exception of the following study listed below:

- Immunotoxicity Study (OPPTS 870.7800) (See Table 4 for more details).

The following data were required as part of the 2009 Permethrin DCI (GDCI-109701-26467). To date, EPA has not received studies to satisfy the following requirements:

- Magnitude of Residue Crop Field Trial Data (OPPTS 860.1500) for cabbage; collards; grass, forage; lettuce, leaf; soybean, forage; and soybean, seed.

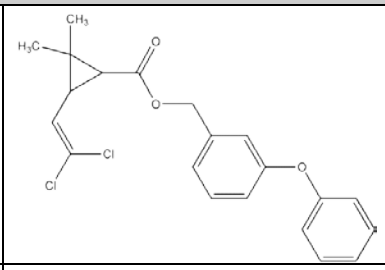
Table 1. Permethrin Nomenclature	
Chemical structure	
Common name	Permethrin
Molecular Formula	$C_{21}H_{20}Cl_2O_3$
Molecular Weight	391.3
IUPAC name	3-phenoxybenzyl (1RS)-*cis*-*trans*-3-(2,2-dichlorovinyl)-2,2- dimethylcyclopropanecarboxylate
CAS name	(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate
CAS #	52645-53-1
PC Code	109701
Current Food/Feed Site Registration	Numerous food/feed crops, livestock, livestock housing and premises, and food-handling establishments

Table 2. Physicochemical Properties of Permethrin		
Parameter	Value	Reference
Boiling point	220 °C (0.05 mm Hg; decomposes)	2001 Farm Chemicals Handbook
Melting point	31 °C 35 °C	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook
pH	4.44 at 20 °C	RD D274107, 7/12/01, S. Mathur
Density, bulk density, or specific gravity	1.229 g/cc 1.190-1.272 specific gravity at 20 °C	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook
Water solubility	0.21 mg/L at 20 °C <1 ppm	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook
Solvent solubility	258 mg/kg in methanol at 25 °C >1000 g/kg in hexane at 25 °C Miscible in most organic solvents except ethylene glycol; soluble in acetone, ethanol, ether, and xylene	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook
Vapor pressure	0.07 mPa at 20 °C <10 Torr at 50 °C	RD D274107, 7/12/01, S. Mathur 2001 Farm Chemicals Handbook
Dissociation constant, pK_a	Not applicable because permethrin is neither an acid nor a base.	
Octanol/water partition coefficient	log P_{OW} = 4.19 at 20 °C	RD D274107, 7/12/01, S. Mathur
UV/visible absorption spectrum	<u>At pH 7</u> λmax 1 = 273 nm, 3.22 log ε λmax 2 = 207 nm, 4.55 log ε <u>At pH <2</u> λmax 1 = 276 nm, 3.24 log ε λmax 2 = 209 nm, 4.43 log ε <u>At pH >10</u> λmax 1 = 272 nm, 3.19 log ε λmax 2 = 212 nm, 4.99 log ε	RD D274107, 7/12/01, S. Mathur

Table 3A. Toxicology Data Requirements for Permethrin		
Test	**Technical**	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes[1]
870.3150 Oral Subchronic (nonrodent)	yes	yes[1]
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	N/A
870.3465 90-Day Inhalation	no	N/A
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	yes
870.6100b 90-Day Neurotoxicity (hen)	no	no
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	yes	no [2]
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
870.7800 Immunotoxicity	yes	no
Special Studies for Ocular Effects		
Acute Oral (rat)	no	no
Subchronic Oral (rat)	no	no
Six-month Oral (dog)	no	no

1. Requirements are satisfied by chronic oral toxicity studies.

2. Based on the Agency's review of existing pyrethroid data, EPA has come to the conclusion that the DNT is not a particularly sensitive study for comparing the sensitivity of young and adult animals to pyrethroid. The science supporting this conclusion can be found in "*Pyrethroids: Evaluation of Data from DNTs & Consideration of Comparative Sensitivity"* (E. Scollon, 1/20/10, D371723), available at http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

Table 3B. Acute Toxicity Profile for Permethrin				
OPPTS Guideline	**Study Type**	**MRID No.**	**Results**	**Toxicity Category**
870.1100	Acute oral toxicity in Rats	242899	LD_{50} = 3580 mg/kg (M) 2280 mg/kg (F)	III
870.1200	Acute dermal toxicity in Rabbits	242899	LD_{50} >2000 mg/kg	III
870.1300	Acute inhalation toxicity in Rats	45804302	LC50 >2.08 mg/L	IV
870.2400	Acute eye irritation in Rabbits	242899	Irritation 24-48 hrs. All cleared by 72 hrs.	III
870.2500	Acute dermal irritation in Rabbits	242899	All irritation cleared by 48 hrs	IV
870.2600	Skin sensitization in Guinea Pigs	EPA Memo *	Non-sensitizer**	Not Applicable

* EPA Memorandum (June 13, 1995) "Permethrin: Review of a series 81-6 dermal sensitization study (guinea pig maximization test) and a series 85-2 dermal penetration study."

** Based on a weight of evidence evaluation of other sensitization study data do not indicate that permethrin should be regulated as a potential sensitizer.

Table 3C. Subchronic, Chronic and Other Toxicity Profile for Permethrin		
Guideline No./ StudyType	**MRID Nos. Doses/Classification**	**Results**
870.3200 21-Day dermal toxicity - Rat	41143801,42653301 Ph III Summ: 92142030 0, 50, 150, 500 mg/kg/day Acceptable/guideline	The systemic NOAEL was 500 mg/kg/day (the highest dose tested), the systemic LOAEL was not established. The dermal LOAEL was 50 mg/kg/day based on skin irritation. A dermal NOAEL was not identified.
870.3465, 82-4 15-Day inhalation toxicity - Rat	00096713 0, 0.0061, 0.042, 0.583 mg/L Acceptable/non-guideline	The LOAEL is 0.583 mg/L in male and female rats based on body tremors and hypersensitivity to noise. The NOAEL is 0.042 mg/L.
870.3700a Prenatal developmental - Rat	40943603 0, 15, 50, 150 mg/kg/day Acceptable/Guideline	The maternal toxicity LOAEL is 150 mg/kg/day based on clinical signs of toxicity and decreased body weight gain and food consumption. The maternal toxicity NOAEL is 50 mg/kg/day.the developmental toxicity LOAEL is 150 mg/kg/day based on decrease in fetal body weights and an increase in the incidence rate of short length extra ribs. The developmental toxicity NOAEL is 50 mg/kg/day.
870.3700b Prenatal developmental - Rabbit	92142091,40943602, 92142036 0, 600, 1200, 1800 mg/kg/day Acceptable/guideline	The maternal toxicity LOAEL is estimated to be <600 mg/kg/day based on decreased body weight gain. The maternal toxicity NOAEL is not identified. The developmental toxicity LOAEL is 1200 mg/kg/day based on increased post-implantation loss, greater numbers of early and late resorptions and an equivocal decrease in ossification of the fore- and hind-limbs. The developmental toxicity NOAEL is 600 mg/kg/day.
870.3800 Reproduction and fertility effects - Rat	00102108 00120271 92142092 92142037 0, 500,1000,2500 ppm (0, 25,50,125 mg/kg/day) Acceptable/guideline	The LOAEL for systemic toxicity is 2500 ppm (125 mg/kg/day) based on tremors observed in the F_0 females, and the F_1 and F_2 males and females. The systemic toxicity NOAEL is 1000 ppm (50 mg/kg/day). The reproductive toxicity NOAEL is ≥2500 ppm (125 mg/kg/day) and the reproductive toxicity LOAEL is not identified. The NOAEL for offspring growth and development is ≥2500 ppm (125 mg/kg/day) and the offspring LOAEL is not identified.
870.4300 Chronic toxicity -Rat	92142123 0, 500, 1000, or 2500 ppm 0, 19.4, 36.9, 91.5 mg/kg/day (M) 0, 19.1, 40.2, 104 mg/kg/day (F) Acceptable/guideline	The chronic toxicity LOAEL is 2500 ppm (91.5 mg/kg/day for males and 104 mg/kg/day for females), based on tremors and hypersensitivity. The NOAEL is 500 ppm (36.9 mg/kg/day for males and 19.4 mg/kg/day for females). No tumor

Table 3C. Subchronic, Chronic and Other Toxicity Profile for Permethrin		
Guideline No./ StudyType	**MRID Nos. Doses/Classification**	**Results**
870.4100b Chronic toxicity - dog	00129600 0,5,100,1000 mg/kg/day (capsule) Acceptable/Guideline	The systemic toxicity LOAEL is 1000 mg/kg/day based on clinical neurotoxic signs and decreased body weight gain and food consumption. The NOAEL is 100 mg/kg/day.
870.4200b Carcinogenicity - mouse	00062806, 92142033 0, 3, 71, 286 mg/kg/day (M) 0, 3, 357, 714 mg/kg/day (F) Acceptable/guideline	There were statistically significant increases in liver adenoma at all doses for males and at mid- and high-doses for females with a significant dose-related trend in both sexes.
870.4200b Carcinogenicity - mouse	00102110, 92142032 0, 26.9, 110.5, 287.2 mg/kg/day (M). 0, 29.8, 124.2, 316.1 mg/kg/day (F) Acceptable/guideline	There was no evidence of significant increase in unusual tumor types. A non-significant increase in lung adenomas in males and in lung adenomas plus carcinomas in females was seen at the highest dose.
870.4200b Carcinogenicity - mouse	45597105 0, 5000 ppm (Females only) (0, 780-807 mg/kg/day) Acceptable/non-guideline	There were significant increases in the incidences of lung bronchioloalveolar adenomas in mice. The increased incidences of basophilic hepatocellular adenoma did not show a relationship to the treatment duration. No progression to carcinoma was observed in the lung or liver.
870.5100 Gene mutation Salmonella typhimurium	41031107 Acceptable/guideline	There were no evidence of increased revertant colonies above control in 5 Salmonella strains up to 5000 µg/plate (solubility limit).
870.5550 Unscheduled DNA	40943604 Acceptable/guideline	There was no evidence of unscheduled DNA synthesis above control up to 10^{-4} M and possibly 10^{-2} M Limits of cytotoxicity).
870.5395 Mouse Bone Marrow Micronucleus	42723302 Acceptable/guideline	There was no evidence that permethrin is clastogenic in the bone marrow cells of mice.
870.6200 Acute Neurotoxicity - Rat	43046301 45657401 Acceptable when considered together	NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
870.6200 Subchronic neurotoxicity - Rat	00071952 2500,3000,3750,4500, 5000, 7500 ppm Acceptable/nonguideline	The systemic and neuro- toxicity LOAEL is 2500 ppm (125 mg/kg) based on clinical signs of toxicity and decreases in body weight gain and food consumption. The systemic and neuro- toxicity NOAEL was not identified for this preliminary study.
870.6200b Subchronic neurotoxicity -Rat	40766807 0, 100, 200, 400 mg/kg/day Acceptable/nonguideline	The systemic LOAEL is 200 mg/kg/day based on tremors and irritability. The systemic NOAEL is 100 mg/kg/day. The NOAEL is > 400 mg/kg/day with respect to morphological and histological changes.
870.6100b Delayed Neurotox - Hen	00112933 approx. 9000 mg/kg (94.9% a.i.) cis:trans 36:58.9 Acceptable/guideline	Oral administration of permethrin does not produce delayed neuropathy in the hen.
870.6100b Delayed Neurotox - Hen	00097426 0, 2000,4000 mg/kg cis:trans 25:75 Acceptable/guideline	Oral administration of permethrin up to 4000 mg/kg does not produce delayed neuropathy in the hen.

Table 3D. Summary of Toxicological Doses and Endpoints for Permethrin for Use in Dietary and Residential Human Health Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Females 13-50 years of age)	**Acute RfD** = No applicable	An appropriate endpoint attributable to a single dose was not identified.	
Acute Dietary (General population including infants and children	Oral NOAEL = **25** mg/kg/day UF = **100** **Acute RfD** = 0.25 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.25 mg/kg/day	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
Chronic Dietary (All populations)	Oral NOAEL= **25** mg/kg/day UF = **100** **Chronic RfD** = 0.25 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.25 mg/kg/day	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
Short- and Intermediate Term Incidental Oral	Oral NOAEL = 25 mg/kg/day	**Residential** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.
Short-, Intermediate-, and Long-Term Dermal	Dermal NOAEL= 500 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**21-Day Dermal Toxicity Study in Rats** LOAEL was not established.
Short-, Intermediate-, and Long-Term Term Inhalation	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.
Cancer (Oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" based on female mouse lung adenoma and/or carcinoma combined tumor rates. Q_1* $(mg/kg/day)^{-1}$ = 9.567×10^{-3}		

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic).

Table 3E. Summary of Toxicological Doses and Endpoints for Permethrin for Use in Occupational Human Health Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Short-, Intermediate-, and Long-Term Dermal	Dermal NOAEL= 500 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**21-Day Dermal Toxicity Study in Rats** LOAEL was not established.
Short-, Intermediate-, and Long-Term Term Inhalation	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.
Cancer (Oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" based on female mouse lung adenoma and/or carcinoma combined tumor rates. Q_1^* $(mg/kg/day)^{-1} = 9.567 \times 10^{-3}$		

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level.

DCI Justification for Immunotoxicity Study

Table 4: Guideline Number: 870.7800 **Study Title: Immunotoxicity - Permethrin**
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.
Practical Utility of the Data
How will the data be used? Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

Table 5. Permethrin International Residue Limits

Summary of US and International Tolerances and Maximum Residue Limits

Residue Definition:

US	Canada		Mexico[2]	Codex[3]
40 CFR 180.378: Plant/Livestock: Combined residues of the insecticide cis- and trans-permethrin isomers [cis-(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] and [trans-(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate]	Plants/Livestock/Dairy commodities: (3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate (For livestock/ dairy commodities calculated on the fat content)			Permethrin (sum of isomers) (fat- soluble)
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[2]	Codex
Alfalfa, forage	20			100 Alfalfa fodder (dry wt)
Alfalfa, hay	45			
Almond	0.05			0.1
Almond, hulls	20			
Artichoke, globe	5.0			
Asparagus	2.0			1
Avocado	1.0			
Broccoli	2.0	0.5		2
Brussels sprouts	1.0	0.5		1
Cabbage	6.0	0.5		5 Cabbage, Savoy, cabbage head, Chinese cabbage (type pe-tsai)
Cattle, fat	1.5	0.1		
Cattle, meat	0.10	0.1		
Cattle, meat byproducts	0.10	0.1		0.1 [4] Edible offal (mammalian)
Cauliflower	0.5			0.5
Cherry, sweet	4.0			
Cherry, tart	4.0			
Corn, field, forage	50			
Corn, field, grain	0.05			2 Cereal grains (Po)
Corn, field, stover	30			100 Maize fodder (dry) dry wt
Corn, pop, grain	0.05			2 Cereal grains (Po)
Corn, pop, stover	30			
Corn, sweet, forage	50			
Corn, sweet, kernel plus cob with husks removed	0.10			0.1 Sweet corn (corn-on-the-cob)
Corn, sweet, stover	30			
Egg	0.10			0.1
Eggplant	0.50			1
Fruit, pome, group 11	0.05	1.0 Apples, pears		50 Apple pomace, Dry; 2 Pome fruits
Garlic, bulb	0.10			
Grain, aspirated fractions	0.50			
Goat, fat	1.5			
Goat, meat	0.10			

Table 5. Permethrin International Residue Limits				
Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
Goat, meat byproducts	0.10			0.1 [4] Edible offal (mammalian)
Hazelnut	0.05			
Hog, fat	0.05			
Hog, meat	0.05			
Hog, meat byproducts	0.05			0.1 [4] Edible offal (mammalian)
Horse, fat	1.5			
Horse, meat	0.10			
Horse, meat byproducts	0.10			0.1 [4] Edible offal (mammalian)
Horseradish	0.50			0.5
Kiwifruit	2.0			2
Leaf petioles subgroup 4B	5.0	5.0 Celery		2 Celery
Leafy greens subgroup 4A	20	20 Leaf lettuce		
Lettuce, head	20	10		2
Milk, fat (reflecting 0.88 ppm in whole milk)	3.0	0.2 Milk; 0.2 Other dairy products		0.1 F
Mushroom	5.0			0.1
Onion, bulb	0.10			
Peach	1.0	1.0 Peaches/Nectarines		
Pepper, bell	0.50	0.5 Peppers		1 Peppers; 10 Peppers Chili, dried
Pistachio	0.10			0.05 Pistachio nuts (*)
Potato	0.05			0.05 (*)
Poultry, fat	0.15	0.1		
Poultry, meat	0.05	0.1		0.1
Poultry, meat byproducts	0.05	0.1		
Sheep, fat	1.5			
Sheep, meat	0.10			
Sheep, meat byproducts	0.10			0.1 [4] Edible offal (mammalian)
Soybean, seed	0.05			0.05 Soya bean (dry) (*); 50 Soya bean fodder (dry wt); 0.1 Soya bean oil, Crude
Spinach	20	20		2
Tomato	2.0	0.5		1
Vegetable, cucurbit, group 9	1.5	0.5 Cucumbers		0.5 Cucumber, Gherkin, Squash summer, Winter squash; 0.1 Melons, except watermelon
Walnut	0.05			
Watercress	5.0			
MRLs with no US equivalent				
Beans		0.5		0.1 Beans (dry)
Blackberries				1
Carrot				0.1

Table 5. Permethrin International Residue Limits				
Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
Citrus fruits				0.5
Coffee beans				0.05 (*)
Common bean (pods and/or immature seeds)				1
Cotton seed				0.5
Cotton seed oil, Edible				0.1
Currants, Black, Red, White				2
Dewberries (including boysenberry and loganberry)				1
Gooseberry				2
Grapes		2.0		2.0
Hops, Dry				50
Kale (including among others:Collards, Curly kale, Scotch kale, thousand-headed kale; not including Marrow-stem				5 (see regional registrations below)
Kohlrabi				0.1
Leek				0.5
Meat (from mammals other than marine mammals)				1 (fat)[4]
Olives				1
Peanut				0.1
Peas, Shelled (succulent seeds)				0.1
Plums		0.5		
Radish, Japanese				0.1
Rape seed		0.5		0.05 (*)
Raspberries, Red, Black				1
Sorghum straw and fodder, Dry				20
Spring Onion				0.5
Stone fruits				2
Strawberry				1
Sugar beet				0.05 (*)
Sunflower seed				1
Sunflower seed oil, crude				1
Sunflower seed oil, edible				1
Tea, Green, Black (black, fermented and dried)				20
Wasabi		0.5		
Wheat bran, Unprocessed				5 (PoP)
Wheat flour				0.5 (PoP)
Wheat germ				2 (PoP)
Wheat wholemeal				2 (PoP)
Completed: M. Negussie; 02/10/2011				

[1] Includes only commodities of interest for this action. Tolerance values should be the HED recommendations and not those proposed by the applicant.

[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[3] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. F = measured in the milk fat. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.

[4] The MRL accommodates external animal treatment.

Table 6: Proprietary Studies Utilized in 2009 Permethrin Risk Assessment	
MRID #	**Title**
44518501	Carbaryl Mixer/Loader/Applicator Exposure Study During Application of RP-2 Liquid (21%) to Fruit Trees and Ornamental Plants. D. Merricks. (1998).
44459801	Carbaryl Mixer/Loader/Applicator Exposure Study During Application of RP-2 Liquid (21%), Sevin Ready to Use Insect Spray or Sevin 10 Dust to Home Garden Vegetables. D. Merricks. (1997).
44439901	Carbaryl Applicator Exposure Study During Application of Sevin 5 Dust to Dogs by the Non-Professional. D. Merricks. (1997).
41054701	Exposure of Applicators to Propoxur During Trigger Pump Spray Application of a Liquid Product: 99100. R. Knarr. (1988).
45250702	Fipronil: Worker Exposure Study During Application of Regent 20GR in Banana Plantation. P. Pontal. (1996).
46601001	Human Exposure During and Following Use of a Pyrethrins/Piperonyl Butoxide/MGK-264 Shampoo Formulation on Dogs. S. Selim. (2005).
46188618	Measurement of Air Concentration, Dermal Exposure, and Deposition of Pyrethrin and Piperonyl Butoxide Following the Use of an Aerosol Spray. S. Selim. (2002).
44658401	Dermal Exposure and Inhalation Exposure to Carbaryl by Commercial Pet Groomers During Application of Adams Carbaryl Flea and Tick Shampoo: Lab Project Number: 97649: 2405Z-60-97-109: 44088. T. Mester. (1998).
N/A	Permethrin transfer from treated cloth to the skin surface; potential for exposure in humans. Journal of Toxicology and Environmental Health, 35: 91-105. H. Snodgrass H. (1992).
46594103	Stroking Test in Dogs After Topical Application of Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot On. T. Bach; R. Krebber. (2002).

Table 7: HED Memoranda Relevant to Registration Review			
Author	**Barcode/TXR #**	**Date**	**Title**
S. Kinard	D313662	03/17/2005	Permethrin. Revised Residue Chemistry Considerations for Reregistration Eligibility Decision (RED) Document.
S. Ary	D325429	02/01/2006	Permethrin. Second Revised Acute, Chronic, and Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision (RED) Document.
C. Smith	D325428	04/04/2006	Permethrin: Third Revision of the Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document.
C. Smith	D357566	04/01/2009	Permethrin: Sixth Revision of the HED Chapter of the Reregistration Eligibility Decision Document (RED).
K. Oo	D386498	03/01/2011	Permethrin: Review of Human Incidents